EXHIBIT L

Remington's PHARMACEUTICAL SCIENCES

A treatise on the theory and practice of pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities and services of the pharmacist as a member of the health team . . . . A textbook and reference work for pharmacists, physicians, and other medical scientists

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wheal. The initial red spot is mostly due to local vasodilatation, and the wheal develops from an increased capillary permeability. The flare is a local phenomenon produced by an axon reflex involving peripheral sensory nerves. Since the flare does not appear in the presence of atrophy or degeneration of the nerve, this reaction has been used as a diagnostic test to distinguish between real and pseudo anesthesia.

When injected intravenously, histamine provokes an increased output of epinephrine from the adrenal medulla as indicated by a secondary rise in blood pressure. Clinical use is made of this action on the adrenals by employing histamine as a test agent in the diagnosis of pheochromocytoma.

Despite the fact that histamine has yet to become established as a therapeutic agent, the several diagnostic uses justify its official recognition.

Uses—The therapeutic uses of histamine are limited. It is employed chiefly as a *diagnostic aid* in testing for the *functional capacity of the gastric glands*. If no acid is secreted following the injection of 0.25 to 0.5 mg (usually as a 1:1000 solution), a true gastric achylia exists.

Histamine is employed in the *diagnosis of pheochromocytoma*. In patients with adrenal medullary tumors, intravenous administration of the compound is followed by a dramatic rise in blood pressure due to the release of excessive quantities of epinephrine and norepinephrine from the neoplasm.

Certain allergic conditions are thought to be the result of the liberation of histamine in the body, especially physical allergies as, for example, cold allergy. Histamine has been employed with questionable success to desensitize such individuals.

The drug has been tried in a variety of other conditions, but its true worth is not yet established. Included in this category are rheumatoid arthritis and Ménière's disease.

Upon local application, Histamine Phosphate causes vasodilatation. It has been incorporated in an ointment base for the treatment of indolent ulcers.

Dose—*Subcutaneous*, **800 mcg** to **2 mg** (the equivalent of 300 to 700 mcg of histamine base); *usual*, **800 mcg** (the equivalent of 300 mcg of histamine base).

Dosage Forms—Injection USP: 100 and 364 mcg and 1 mg/ml, 1 and 5 mg/5 ml, 3.64 and 10 mg/10 ml, 2 mg/20 ml, 11 mg/30 ml.

Antihistamines

Following the suggestion by Dale and Laidlaw in 1911 that the symptoms of histamine shock resembled those in anaphylaxis many experimenters added findings tending to substantiate the concept that release of histamine from the tissues is responsible for the anaphylactic reaction. It is true that some of the manifestations of anaphylaxis cannot be explained by histamine effect, but it was argued that histamine is at least the major mechanism. The histamine concept was gradually adopted to explain the allergic reaction in man after Lewis, in 1924, claimed that the histamine effects in man were identical with those of allergy. Many attempts were then made in animals and man to raise the tolerance to histamine by injections of the latter. The preponderance of evidence indicates that a tolerance to histamine only infrequently can be acquired in that manner. Evidence that obtaining such tolerance in man can be obtained by the administration of conjugated histamine (histamine-azo-protein or *Hapamine*) has not been established.

Although many substances had been previously demonstrated to antagonize responses to histamine and certain manifestations of antigen–antibody reactions, it was not until 1942 that sufficiently specific and nontoxic agents became available for this action to be of clinical importance. As a result of intensive research in this field, a very large number of effective agents are now on the market. These differ in antihistaminic potency, length of action, untoward effects, toxicity, and cost. A knowledge of these factors is essential for proper drug selection.

Uses—All presently available *antihistamines* (*antihistaminics* or antihistaminic agents) are effective in preventing histamine shock in guinea pigs, bronchospasm induced in guinea pigs by nebulized histamine solutions, whealing on the skin, and many other responses to histamine. The hypotension induced by histamine is more difficult to block and the increased salivation and gastric secretion are not inhibited. The antihistamines also have antianaphylactic properties in large doses and are antipruritic and analgesic. Some have bowel or bladder smooth muscle antispasmodic action; some produce sedation and others central nervous system stimulation.

Clinically, the antihistamines are most effective in *seasonal vasomotor rhinitis* (especially during the earlier part of the season), *acute urticaria* and *acute reactions to sulfonamides, penicillin, and other medicaments*. However, it must be remembered that they produce only symptomatic relief and do not correct the underlying disorder. The relief lasts only as long as medication continues or as the disorder is corrected by other means. These agents are also frequently effective in treating various types of *contact dermatitis*, certain features of *serum reactions*, *pruritus vulvæ*, *pruritus ani*, and *insect bites*. Chronic rhinitis, asthma, and erythema nodosa-type of sensitivity reactions are rarely benefited. Pruritus is frequently relieved by the local application of antihistamines, probably to a large extent because of their local anesthetic properties. Certain antihistamines are useful in the prevention and treatment of motion sickness (see page 807). Claims have been made for the efficacy of antihistamine therapy of the common cold, but carefully controlled clinical studies fail to support the claims; however, certain *nasopharyngeal allergic conditions* that simulate the common cold are benefited.

The more severe the affection the larger the dose of antihistamine required and the less the chance of obtaining benefit. These agents may be employed to supplement desensitization procedures, and their administration one hour prior to injection of specific antigens may allow the administration of larger doses of antigen and thus speed the process of desensitization. The response to antihistamines is usually not as rapid or complete as that to epinephrine or intravenous aminophylline, but some workers have found that intravenous administration of antihistamines is of definite value in combating acute allergic episodes. Certain antihistamines cannot be given parenterally because of strong irritating properties.

The sedative antihistamines are sometimes used as

Alcoholic solutions of volatile principles as employed in pharmacy may be regarded as a development of the perfume industry. It was discovered that alcoholic solutions of volatile oils possessed more delicate and fragrant odors than the pure oil itself, and as more aromatic principles were discovered or synthesized, experimentation resulted in the production of innumerable blends to satisfy every individual desire.

The formula and procedure given for Aromatic Ammonia Spirit NF illustrate this method of preparation.

Aromatic Ammonia Spirit NF

Ammonium Carbonate, in translucent pieces	34 Gm
Strong Ammonia Solution	36 ml
Lemon Oil	10 ml
Lavender Oil	1 ml
Myristica Oil	1 ml
Alcohol	700 ml
Purified Water, a sufficient quantity	
To make	1000 ml

Dissolve the ammonium carbonate in the strong ammonia solution and 195 ml of purified water by gentle agitation, and allow the solution to stand for 12 hours. Dissolve the oils in the alcohol, contained in a graduated bottle or cylinder, and gradually add the ammonium carbonate solution and enough purified water to make the product measure 1000 ml. Set the mixture aside in a cool place for 24 hours, occasionally agitating it, and then filter, using a covered funnel.

The spirit is a respiratory stimulant and is administered by inhalation of the vapor as required. It is marketed in suitable tight, light-resistant containers but is also available in a single-dose glass vial wrapped in a soft cotton envelope. The vial is easily broken; the cotton acts as a sponge for the spirit.

Ammonium carbonate is a mixture of ammonium bicarbonate and ammonium carbamate (NH_2COONH_4). The carbamate reacts with water to form the carbonate.

$$NH_2COONH_4 + H_2O \rightarrow 2NH_4CO_3$$

An ammonium carbonate solution is, therefore, a solution of ammonium bicarbonate and ammonium carbonate in water. However, it decomposes in water, the decomposition products being ammonia, carbon dioxide, and water. The stability of the spirit is improved by the addition of strong ammonia solution. This represses the hydrolysis of ammonium carbonate and, in this way, decreases the loss of dissolved gases.

Solution with Maceration—In this procedure, leaves of the drug are macerated in purified water to extract water-soluble matter. They are then expressed, and the moist macerated leaves are added to a prescribed quantity of alcohol. The volatile oil is added to the filtered liquid. Peppermint Spirit NF is made by this process. Peppermint Spirit BPC 1968 differs from the official product in that it is a solution of the volatile oil in alcohol only. The concentration of volatile oil in the final product is about the same but the official preparation possesses a green color. The ready availability of soluble chlorophyll and other coloring agents has led to the frequent suggestion that a more uniform product could be obtained through their use. However, these agents cannot be used in preparing the official article.

The formula and procedure given for Peppermint Spirit NF (page 813) illustrate this method of preparation.

Chemical Reaction—No official spirits are prepared by this process. Ethyl nitrite is made by the action of sodium nitrite on a mixture of alcohol and sulfuric acid in the cold. This substance is then used to prepare Ethyl Nitrite Spirit, a product which is no longer official.

Distillation—Brandy and Whisky are made by distillation. The latter product is derived from the fermented mash of wholly or partially germinated malted cereal grains and the former from the fermented juice of ripe grapes.

Incompatibilities—Spirits are, for the most part, preparations of high alcoholic strength and do not lend themselves well to dilution with aqueous solutions or liquids of low alcoholic content. The addition of such a solution invariably causes a separation of some of the material dissolved in the spirit, the evidence of separation being a turbidity which, in time, may disappear as distinct layering occurs. Salts may be precipitated from their aqueous solutions by the addition of spirits due to their lesser solubility in alcoholic liquids.

Some spirits show incompatibilities peculiar to the ingredients which they contain. For example, Aromatic Ammonia Spirit NF cannot be mixed with aqueous preparations containing alkaloids (eg, codeine phosphate). An acid–base reaction (ammonia–phosphate) occurs and, if the alcoholic content of the final mixture is too low, codeine will precipitate out of solution.

Sprays

Sprays are solutions of various drugs in oily or aqueous vehicles and are applied to the mucous membrane of the nose and throat by means of an atomizer or nembulizer. The spray device should produce relatively coarse droplets if the action of the drug is to be restricted to the upper respiratory tract. Fine droplets tend to penetrate farther into the respiratory tract than is desirable.

Many of the older sprays contained menthol, thymol, camphor, methyl salicylate, and ephedrine dissolved in light liquid petrolatum. The use of light liquid petrolatum as a vehicle has, however, been severely criticized. There are two basic reasons for this. The first relates to the danger of lipoid pneumonia from the use of these oily preparations. Other reports have indicated that such sprays retard the normal ciliary activity on the nasal mucosa. In addition to this, the basic formulations have been criticized because of the instability of ephedrine in light liquid petrolatum.[15]

On the basis of the above reports, aqueous sprays which are isotonic with nasal secretions and of approximately the same pH are to be preferred. Such sprays may contain antibiotics, antihistamines, vasoconstrictors, alcohol, and suitable solubilizing and wetting agents. The pharmacist will handle many commercial preparations that comply with the basic definition given above and that help to alleviate the nasal congestion due to the common cold. For example, one of these contains chlorpheniramine maleate, phenylephrine hydrochloride, and gramicidin. Another is described as an isotonic, buffered (pH 6.2), aqueous solution containing phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pheniramine maleate, and chlorobutanol. Most of the highly advertised sprays are marketed either in standard dropper bottles or in plastic squeeze units.

Ayerst Laboratories market a throat spray containing anise oil (0.6%), cassia oil (0.1%), pyrilamine maleate (0.05%), antipyrine (0.3%), methyl salicylate (0.05%), menthol (0.1%), sodium caprylate (0.5%), alcohol (1%), glycerol (2%), and methylrosaniline chloride. The "Spray-O-Mizer" squeeze bottles are a

convenient device for delivering this spray into the throat cavity.

Toothache Drops

Toothache drops are preparations used for the temporary relief of toothache by application of a small pledget of cotton saturated with the product into the tooth cavity. Clove oil and mixtures of phenol with camphor or creosote are probably the most frequently used toothache remedies. When phenol, creosote, or volatile oils are dissolved in paraffin to which a few filaments of cotton have been added, and the mixture molded into sticks, a preparation referred to as *dental wax* is formed.

These preparations are no longer recognized by either of the compendia. Furthermore, dentists do not recommend the use of toothache drops if the patient has ready access to adequate dental services. The preparations may damage the gums and produce complications more severe than the original toothache. However, many areas do not have adequate dental services and the pharmacist will, of necessity, handle these preparations. If such is the case, the pharmacist should warn the patient of the possible hazards associated with the use of these products.

Toothache Drops NF XI contain 25 Gm of chlorobutanol in sufficient clove oil to make the product measure 100 ml. Another formulation contains creosote (50 ml), clove oil (50 ml), and chloroform (50 ml).

Emulsions

An emulsion is a two-phase system and is prepared by combining two immiscible liquids, one of which is uniformly dispersed throughout the other and consists of globules that have diameters equal to or greater than those of the largest colloidal particles. The globule size is, of course, critical and must be such that the system achieves a maximum of stability. However, even under the best of conditions, separation of the two phases will occur unless a third substance, an *emulsifying agent*, is incorporated into the original product. The basic emulsion must, therefore, contain three components but the products of commerce may consist of a number of therapeutic agents dissolved in either of the two phases of the preparation.

Most emulsions are so prepared as to incorporate an aqueous phase into a nonaqueous phase (or *vice versa*). However, it is possible to prepare emulsions that are basically nonaqueous in character. For example, McMahon, *et al*,[16] investigated the emulsifying effects of twelve anionic and five cationic surfactants on the nonaqueous immiscible system, glycerin and olive oil. They observed that certain amines and three cationic agents produced stable emulsions of this system. This broadening of the basic definition for the term *emulsion* is evident in the USP.

"An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. The dispersed liquid is known as the internal phase, whereas the dispersion medium is known as the external or continuous phase. When oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water (O/W) emulsion. Conversely, when water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil (W/O) emulsion."

The USP continues the definition by describing and discussing the effects of various emulsifying agents. These substances fall into three broad groups.[17]

Natural Emulsifying Agents—These substances may be derived from either animal or vegetable sources. Examples of those obtained from the former source are gelatin, egg yolk, casein, wool fat, and cholesterol. Acacia, tragacanth, chondrus, and pectin are representative of those obtained from vegetable sources.

Finely Divided Solids—Examples of emulsifying agents of this type are bentonite, magnesium hydroxide, aluminum hydroxide, and magnesium trisilicate.

Synthetic Emulsifying Agents—This group may be further subdivided into the anionic, cationic, and nonionic agents. Examples of these three types of emulsifying agents are, in order of presentation, sodium lauryl sulfate, benzalkonium chloride, and polyethylene glycol 400 monostearate.

Many of these emulsifying agents are described in greater detail in Chapter 71 on *Pharmaceutical Necessities*, page 1344.

The NF suggests that only O/W emulsions are suitable for oral use because these are water-miscible and thus their oiliness is masked. This compendium gives specific directions for the preparation of emulsions utilizing gelatin as an emulsifying agent. These preparations are based on either types A or B gelatin. Type A gelatin is prepared from acid-treated precursors and is used at a pH of about 3.2. It is incompatible with anionic emulsifying agents such as the vegetable gums. The following formula is recommended:

Gelatin (Type A)	8.0 Gm
Tartaric Acid	0.6 Gm
Flavor as desired	
Alcohol	60.0 ml
Oil	500.0 ml
Purified Water, to make	1000.0 ml

Add the gelatin and the tartaric acid to about 300 ml of purified water, allow to stand for a few minutes, heat until the gelatin is dissolved, then raise the temperature to about 98°, and maintain this temperature for about 20 minutes. Cool to 50°, and add the flavor, the alcohol, and sufficient purified water to make 500 ml. Add the oil, agitate the mixture thoroughly, and pass it through a homogenizer or a colloid mill until the oil is completely and uniformly dispersed.

This emulsion cannot be prepared by trituration or by the use of the usual stirring devices.

Type B gelatin is prepared from alkali-treated precursors and is used at a pH of about 8.0. It may be used with other anionic emulsifying agents but is incompatible with the cationic types. If the emulsion contains 50% oil, 5 Gm of Type B gelatin, 2.5 Gm of sodium bicarbonate, and sufficient tragacanth or agar should be incorporated into the aqueous phase so as to yield 1000 ml of product of the required viscosity.

The emulsion type (O/W or W/O) is of lesser significance if the final preparation is to be applied to the skin. If there are no breaks in the skin, a W/O emulsion can be applied more evenly since the skin is covered with a thin film of sebum. The latter substance favors the oily phase and contributes to the ease of application. The choice of emulsion type will, however, depend on many other factors. This is particularly true for those preparations which have basic cosmetic characteristics. It may be advantageous to formulate an O/W emulsion if ease of removal is an important consideration to the patient.

Very few emulsions are now included in official compendia and the BPC 1968. Mineral Oil Emulsion is described in the NF. The BPC 1968 lists Liquid Paraffin